

REFERENCE NO.

18

In re application of: Lawrence R. McGee, et al.
Application No.: 10/719,997
Filing Date: November 20, 2003
Attorney Docket No.: 018781-006330US

THIS PAGE BLANK (USPTO)



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C08L 53/00	A2	(11) International Publication Number: WO 00/12623 (43) International Publication Date: 9 March 2000 (09.03.00)
(21) International Application Number: PCT/EP99/06219 (22) International Filing Date: 25 August 1999 (25.08.99) (30) Priority Data: 9818914.5 28 August 1998 (28.08.98) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TX8 9EP (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): ROUTLEDGE, Carol [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). (74) Agent: WATERS, David, Martin; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: USE (57) Abstract <p>Use of 5-HT₆ receptor antagonists for the preparation of medicaments for the treatment of Parkinson disease.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

Use

5 The present invention relates to the use of 5-HT₆ receptor antagonist compounds in the treatment of certain CNS disorders. More particularly the invention relates to the use of such compounds in the treatment of Parkinson's disease.

10 Parkinson's Syndrome refers to a collection of neurodegenerative diseases that are characterised by a disturbance of voluntary movement, and which includes both Idiopathic Parkinson's disease and Multiple System Atrophy. Typical features of these diseases are that muscles become stiff and sluggish, movement becomes clumsy and difficult and uncontrollable rhythmic twitching of groups of muscles produces characteristic shaking or tremor. Parkinson's disease is also associated with cognitive dysfunction and, in a proportion of cases, concurrent dementia. These conditions are believed to be caused by extensive degeneration of the dopaminergic nigrostriatal tract.

15 The absence of adequate release of the chemical transmitter dopamine during neuronal activity thereby leads to the Parkinsonian symptomatology.

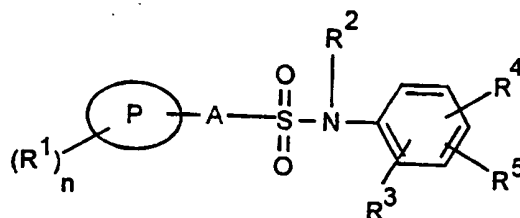
WO 98/27081, WO 98/27058 and WO 99/02502 all disclose compounds that are said to possess 5-HT₆ receptor antagonist activity. These compounds are alleged to be of use in the treatment of various CNS disorders. EPA 0815861 and EP 0930302 disclose sulphonamide and sulphone compounds respectively that are to said to possess 5-HT₆ receptor antagonist activity and are claimed to be useful in the treatment of various CNS disorders including Parkinson's disease. EP 0299602B1 discloses certain indolone derivatives that are useful in the treatment of Parkinson's disease and, advantageously, have anti-depressant and anxiolytic effects.

25 It has now been found that certain compounds, known in the art as 5-HT₆ receptor antagonists, selectively increases activity of the nigrostriatal pathway and consequently have utility in the treatment of Parkinson's disease. In addition, the compounds of the present invention have additional effects on the central nervous system, namely, cognitive effects. In particular, the cognitive effects of the compounds of the present invention are perceived to be advantageous as patients receiving current therapies often also need to take separate medication for the treatment of cognitive dysfunction and dementia. The presence of such qualities as a single compound may therefore reduce the need for such separate therapies.

35 The present invention therefore provides, in a first aspect, the use of a compound having 5-HT₆ receptor antagonist activity in the manufacture of a medicament for use in the treatment of Parkinson's Disease characterized in that the compound having 5-HT₆

receptor antagonist activity is selected from the group consisting of a compound of formula (A), (B) or (C)

Compound of Formula (A)

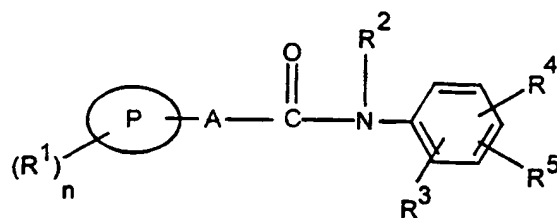


(A)

wherein:

- P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;
- A is a single bond, a C_{1-6} alkylene or a C_{1-6} alkenylene group;
- R^1 is halogen, C_{1-6} alkyl optionally substituted by one or more halogen atoms, C_{3-6} cycloalkyl, COC_{1-6} alkyl, C_{1-6} alkoxy, OCF_3 , hydroxy, hydroxy C_{1-6} alkyl, hydroxy C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, C_{1-6} alkanoyl, nitro, amino, C_{1-6} alkylamino or di C_{1-6} alkylamino, cyano or R^1 is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;
- n is 0, 1, 2, 3, 4, 5 or 6,
- R^2 is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl;
- R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$;
- R^4 is $-X(CH_2)_pR^6$ where X is a single bond, CH_2 , O , NH or $N-C_{1-6}$ alkyl and p is 0 to 6 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and
- R^5 is hydrogen, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, hydroxy, hydroxy C_{1-6} alkyl, hydroxy C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, C_{1-6} alkanoyl, nitro, trifluoromethyl, cyano or aryl.

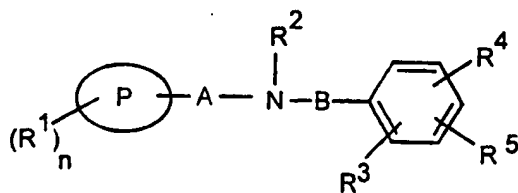
30 Compounds of Formula (B)



(B)

where $R^1 - R^5$, P, A and n are as defined in formula (A)

5 Compounds of Formula (C)



(C)

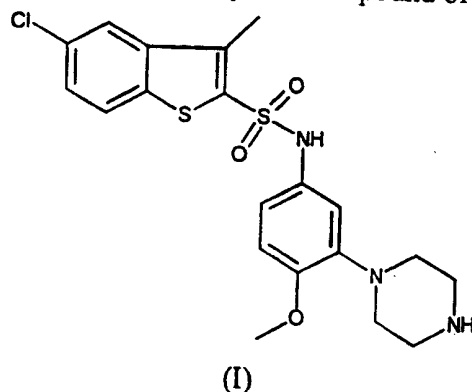
wherein:

- 10 P is phenyl, naphthyl, anthracenyl, a bicyclic heterocyclic ring, a tricyclic heteroaromatic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;
 A is a single bond, a C_{1-6} alkylene or a C_{1-6} alkenylene group;
 B is SO_2 ;
- 15 R^1 is halogen, C_{1-6} alkyl optionally substituted by one or more fluorine atoms, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkanoyl, C_{1-6} alkoxy, OCF_3 , hydroxy, hydroxy C_{1-6} alkyl, hydroxy C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, nitro, cyano, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_{1-6} alkyl or optionally substituted phenyl, SR^{11} where R^{11} is as defined above or R^1 is optionally substituted phenyl,
- 20 naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur, or R^1 together with a second R^1 substituent forms a group $-O-CH_2-O-$, OCH_2CH_2O- , $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$,
 n is 0, 1, 2, 3, 4, 5 or 6;
- 25 R^2 is hydrogen, C_{1-6} alkyl, aryl C_{1-6} alkyl or together with group P form a 5 to 8 membered ring optionally substituted with one or more C_{1-6} alkyl groups;
 R^3 is hydrogen, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkanoyl, C_{1-6} alkoxy optionally substituted with one or more fluorine atoms, hydroxy, hydroxy C_{1-6} alkyl, hydroxy C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, , nitro, trifluoromethyl, cyano or aryl or
- 30 together with the group R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6} alkyl groups;

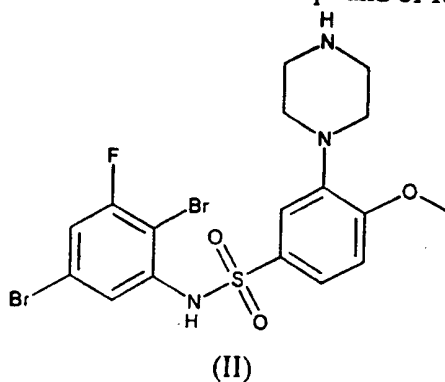
- R^4 is $-X(CH_2)_p-R^6$ where X is a single bond, CH_2 , O, NH or N-alkyl and p is 0 to 6 and R^6 is an optionally substituted 4- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and
- 5 R^5 is a group R^3 or together with R^3 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6} alkyl groups.

The preferred compounds for use in this invention demonstrate greater than 100-fold selectivity for 5-HT₆ receptors over other binding sites within the CNS, in particular, other 5-HT receptor sub-types and dopaminergic receptors. The selectivity of the compounds of this invention for 5-HT₆ receptors can be determined using binding assays methods which are well known to those skilled in the art.

Particularly preferred compounds of this invention include 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (Example 83 in WO 98/27081), that is to say, the compound of formula (I)



and *N*-(2,5-Dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide (Example 140 in WO 99/02502) that is to say, the compound of formula (II)



It will be apparent to those skilled in the art that compounds of formulas (A), (B) and (C) may form acid addition salts. Suitable examples include pharmaceutically

acceptable salts such as maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic. Suitably, a compound of formula (I) or formula (II) is used as the hydrochloride salt.

5 Certain compounds of formulas (A), (B) and (C) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

The compounds of formulas (A), (B) and (C) and their pharmaceutically acceptable salts can be prepared by the methods described in WO 98/27081, WO 10 98/27058 and WO 99/02502 respectively.

The compounds for use in this invention can be evaluated for anti - Parkinson activity using procedures known to those skilled in the art such as the MPTP treated marmoset model.

15 The compounds for use in this invention are expected to have utility in treating any condition characterized by degeneration of the dopaminergic nigrostriatal tract. Consequently, these compounds will be useful in the treatment of both Idiopathic Parkinson's disease and Multiple System Atrophy. Multiple System Atrophy includes olivopontocerebellar atrophy, striato-nigral degeneration type and Shy-Drager type atrophy.

20 The present invention further provides a method of treatment of Parkinson's Disease and other related disorders which comprises administering to a host in need thereof an effective amount of a compound of formula (A), (B) or (C) or a pharmaceutically acceptable salt thereof.

25 It will be appreciated by those skilled in the art that the compounds according to this invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, by co-administration with other anti-Parkinson's agents. Examples of such include levodopa or a dopamine agonists, and in particular, those described in EP 0299602B1.

30 When used in therapy, the compounds of formula (A), (B) or (C) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

35 A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

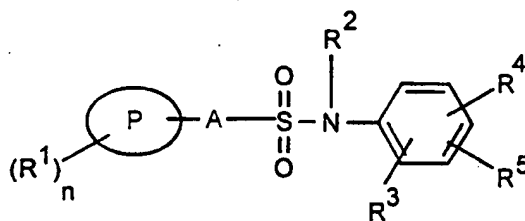
5 Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs. or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if
10 desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either
15 suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral
20 suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to
25 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg. and such unit doses may be administered more than once a
30 day, for example two or three a day. Suitably the compounds for use in this invention will be administered for a period of continuous therapy.

Claims:

1. The use of a compound having 5-HT₆ receptor antagonist activity in the manufacture of a medicament for use in the treatment of Parkinson's Disease
- 5 characterized in that the compound having 5-HT₆ receptor antagonist activity is selected from the group consisting of a compound of formula (A), (B) or (C)

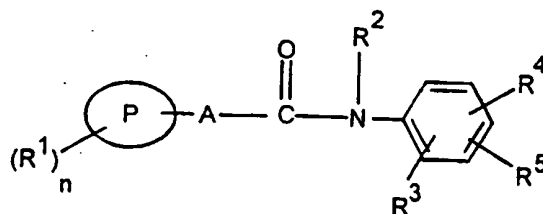
Compound of Formula (A)

(A)

wherein:

- P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;
- 15 A is a single bond, a C₁₋₆alkylene or a C₁₋₆alkenylene group;
- R¹ is halogen, C₁₋₆alkyl optionally substituted by one or more halogen atoms, C₃₋₆cycloalkyl, COC₁₋₆alkyl, C₁₋₆alkoxy, OCF₃, hydroxy, hydroxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkoxy, C₁₋₆alkanoyl, nitro, amino, C₁₋₆alkylamino or diC₁₋₆alkylamino, cyano or R¹ is phenyl, naphthyl, a bicyclic
- 20 heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;
- n is 0, 1, 2, 3, 4, 5 or 6,
- R² is hydrogen, C₁₋₆ alkyl or aryl C₁₋₆ alkyl;
- R³ is a group R⁵ or together with R⁵ forms a group (CH₂)₂O or (CH₂)₃O or R³ is linked
- 25 to R² to form a group (CH₂)₂ or (CH₂)₃;
- R⁴ is -X(CH₂)_p-R⁶ where X is a single bond, CH₂, O, NH or N- C₁₋₆ alkyl and p is 0 to 6 and R⁶ is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R⁶ is NR⁷R⁸ where R⁷ and R⁸ are independently hydrogen, C₁₋₆ alkyl or aryl C₁₋₆ alkyl; and
- 30 R⁵ is hydrogen, halogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkoxy, hydroxy, hydroxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkoxy, C₁₋₆alkanoyl, nitro, trifluoromethyl, cyano or aryl.

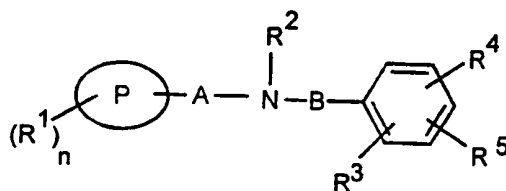
Compounds of Formula (B)



(B)

where $R^1 - R^5$, P, A and n are as defined in formula (A)

5 Compounds of Formula (C)



(C)

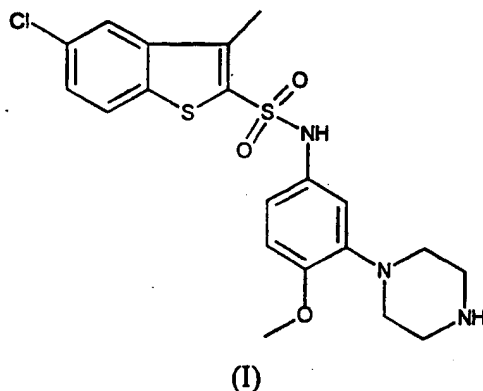
wherein:

- 10 P is phenyl, naphthyl, anthracenyl, a bicyclic heterocyclic ring, a tricyclic heteroaromatic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;
 A is a single bond, a C_{1-6} alkylene or a C_{1-6} alkenylene group;
 B is SO_2 ;
- 15 R^1 is halogen, C_{1-6} alkyl optionally substituted by one or more fluorine atoms, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkanoyl, C_{1-6} alkoxy, OCF_3 , hydroxy, hydroxy C_{1-6} alkyl, hydroxy C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, nitro, cyano, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_{1-6} alkyl or optionally substituted phenyl, SR^{11} where R^{11} is as defined above or R^1 is optionally substituted phenyl,
- 20 naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur, or R^1 together with a second R^1 substituent forms a group $-O-CH_2-O-$, OCH_2CH_2O- , $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$,
 n is 0, 1, 2, 3, 4, 5 or 6;
- 25 R^2 is hydrogen, C_{1-6} alkyl, aryl C_{1-6} alkyl or together with group P form a 5 to 8 membered ring optionally substituted with one or more C_{1-6} alkyl groups;
 R^3 is hydrogen, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkanoyl, C_{1-6} alkoxy optionally substituted with one or more fluorine atoms, hydroxy, hydroxy C_{1-6} alkyl, hydroxy C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, . nitro, trifluoromethyl, cyano or aryl or
- 30 together with the group R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6} alkyl groups;

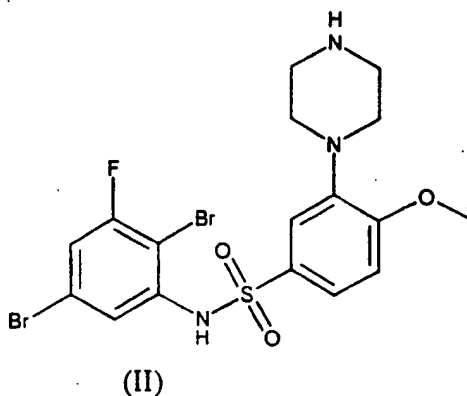
R^4 is $-X(CH_2)_p-R^6$ where X is a single bond, CH_2 , O , NH or N -alkyl and p is 0 to 6 and R^6 is an optionally substituted 4- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and

- 5 R^5 is a group R^3 or together with R^3 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6} alkyl groups.

2. The use according to claim 1 wherein the 5-HT₆ receptor antagonist is the compound of formula (I) - 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide or a pharmaceutically acceptable salt thereof
- 10



- 15 3. The use according to claim 1 wherein the 5-HT₆ receptor antagonist is the compound of formula (II) - *N*-(2,5-Dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide or a pharmaceutically acceptable salt thereof



- 20 4. A pharmaceutical composition for use in the treatment of Parkinson's Disease which comprises a compound described in any one of claims 1 - 3 and a pharmaceutically acceptable carrier.

THIS PAGE BLANK (USPTO)